Author: Ewe, See Hooi
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General introduction and outline of the thesis

The prevalence of moderate or severe aortic valve (AV) disease, namely aortic regurgitation (AR) and aortic stenosis (AS), has been estimated as 0.9% in the largest population-based study from the United States.[1] The prevalence of AV disease rose strikingly with age, which is very low (<1%) before the age of 65, and increases to 2.3% for the ages between 65-74, and to 4.8% after the age of 75.[1] Importantly, moderate or severe valvular diseases are not benign but have profound consequences, with cardiac chamber remodeling on echocardiographic examinations (characteristic of volume or pressure overload) and are associated with excess mortality (relative risk of death was 1.36), after adjusted for coronary artery diseases and comorbid conditions despite the availability of surgical valve repair or replacement in the large population-based study.[1] Therefore, the associated excess risk underscores the importance of accurate detection of valvular diseases. In this regard, advanced cardiac imaging plays a critical role in the early diagnosis and recognition, as well as the detection of its deleterious effect on myocardial function, which is the key to improving prognosis, as prompt referral for valve intervention will interrupt and alter the natural history of AV diseases. Therefore beyond the assessment of chamber dimensions or left ventricular (LV) function, conventionally by ejection fraction (EF) assessment, the evaluation of myocardial tissue deformation and strain may help refine risk stratification and decision-making process in patients with AV diseases.

In the Euro Heart Survey, the most common valvular diseases referred to hospital were AV diseases (44%), and AS accounted for the majority (34%).[2] Similarly, valve interventions were performed mostly for AS (47%), and the predominant etiology was degenerative (82%).[2] Therefore, the majority of AS were in the elderly population, affecting 56% in aged ≥70 and 14% were aged ≥80, in whom there are associated increased rates of comorbidities. In the Euro Heart Survey that analyzed the elderly patients with AS, 33% were not referred for surgery, with impaired LV ejection fraction and old age as the main reasons that determine the decision making.[3] Until recently, AVR was the only definitive therapy but many elderly patients are considered high risk surgical candidates. Conversely, if symptomatic AS is left untreated, the prognosis is dismal with an average survival of 2 to 3 years.[4] Thus, there is a need for alternative treatment for AS, and transcatheter aortic valve implantation (TAVI) is a proven effective therapy in AS patients with extreme or high operative risk, with acceptable mortality and complication rates.[5,6] Besides technical advances and procedural experience, accurate patient selection is the key to achieve high success rates and low complications rates with TAVI. Multimodality imaging plays a crucial role in patient selection, guiding the procedure and evaluation of the immediate and long-term results after TAVI.

Transthoracic echocardiography is the primary imaging modality for the diagnosis and assessment of its severity in AV disease, as well as to assess its prognosis by its hemodynamic consequences on the LV. There are many reasons why echocardiography is the preferred modality over the other modalities, due to its ability to provide real-time comprehensive evaluation of the anatomic and physiologic information of all valves, including the aorta and ventricular functions, and its non-invasiveness and wide availability which allows for serial assessment. Current guidelines for intervention in patients with AV disease are based on the presence or absence of symptoms, as well as 2-dimensional (2D) echocardiographic parameters such as the LV size (LV dimensions) and LV function (LVEF).[5,6] However, conventional 2D echocardiography has several limitations and is less reproducible as it is affected by foreshortened apical views and the reliance on geometric assumptions for the calculation of LV volumes and EF.[7]

Regarding the assessment of valvular regurgitation, although it is recommended to quantify the severity of regurgitation,[8,9] this quantitative approach remains challenging in clinical practice due to multiple computations and assumptions inherent in its derivation using the proximal isovelocity surface area (PISA) method.[9] Yet, the widely used conventional semi-quantitative approach of assessment by color flow Doppler is not endorsed, as it is influenced by hemodynamic flow factors.[8,9] Recent advances in echocardiography, in particular, 3-dimensional (3D) echocardiography may have overcome some of the above-mentioned limitations by permitting direct visualization and measurement of the regurgitant orifice area, without the need for additional computation or geometric assumptions.[10]

In addition, the advent of novel 2D speckle tracking echocardiography (STE) as a new, angle independent technique to evaluate myocardial deformation and strain, have recently been reported to be clinically useful and reproducible.[11] In this respect, the most commonly used measure of LV global systolic function is the global longitudinal strain (GLS), which has been shown to be an incremental predictor of adverse events, beyond LVEF.[12, 13] Moreover, impaired GLS strain may also predict worse outcomes after valve surgery in patients with valvular regurgitation.[14, 15]

Currently, the introduction of TAVI has revolutionized treatment of patients with symptomatic severe AS. In inopertable patients, TAVI has been shown to significantly improve survival over medical therapy.[16] Therefore, TAVI is now a class I recommendation in patients with severe AS and extreme operative risk.[5, 6] Moreover, in patients with high operative risk, TAVI can be considered a viable alternative to surgical aortic valve replacement (SAVR) when TAVI is favored after a multidisciplinary Heart Team assessment,[5,6] as randomized trials have demonstrated that TAVI is non-inferior to SAVR,[17] and is associated with significantly higher one-year survival rate than SAVR.[18] Unlike SAVR where direct inspection is possible, TAVI mandates detailed pre-procedural planning and careful patient and prosthesis selection with the use of multimodality imaging of the AV, aortic root and peripheral arteries, for optimal procedural success. In addition, cardiac imaging plays a key role in the understanding of mechanisms of complications post-TAVI, and provides systematic evaluation and monitoring of the post-procedural results.

THREE-DIMENSIONAL ECHOCARDIOGRAPHY IN AORTIC VALVE DISEASE

Currently, 3D echocardiography are readily available and recent advances have permitted real-time visualization of the entire cardiac structures from any imaging plane. This is a major innovation in the field of cardiovascular ultrasound, offering superior imaging to conventional 2D echocardiography. The clinical usefulness of 3D echocardiography has been demonstrated in: 1) the evaluation of LV volumes and EF[19]; 2) the ability to present unlimited views of heart valves and intracardiac structures using 3D TEE, as it offers superior spatial resolution and 3D anatomic definition, and thus it is the recommended primary imaging modality for guiding transcatheter interventions and for device sizing[20]; 3) the volumetric assessment of regurgitant lesions using 3D color Doppler, with direct quantification by planimetry of the 3D color regurgitation jet (Figure 1), irrespective of a non-circular orifice area or eccentric jet, typically seen in patients with functional mitral regurgitation.[21, 22]

NOVEL IMAGING MODALITIES TO ASSESS LV DEFORMATION

Recently, myocardial strain imaging is proposed as a more sensitive technique to assess the contractile properties of the myocardium, by evaluating the active deformation of the myocardium in all 3 planes of cardiac motion, without being influenced by the tethering or translational cardiac motion. In contrast to previous technique of assessment using Tissue Doppler imaging that is angle-dependent on ultrasound insonation, the novel 2D STE overcomes this by tracking frame-by-frame of the national acoustic markers (the so-called speckles) on gray-scale images and permits measurement of deformation based on excursion between individual speckles throughout the cardiac cycle (Figure 2).[23, 24] In most early disease process, the subendocardial fibers are preferentially affected, and thus the impairment of longitudinal function may occur with preservation of circumferential and radial function.[25] The GLS, as a marker of subendocardial function, has been shown to be incremental and superior to resting LVEF[12, 13] Therefore, the conventional global measures of LV systolic function (such as LVEF, which is used to

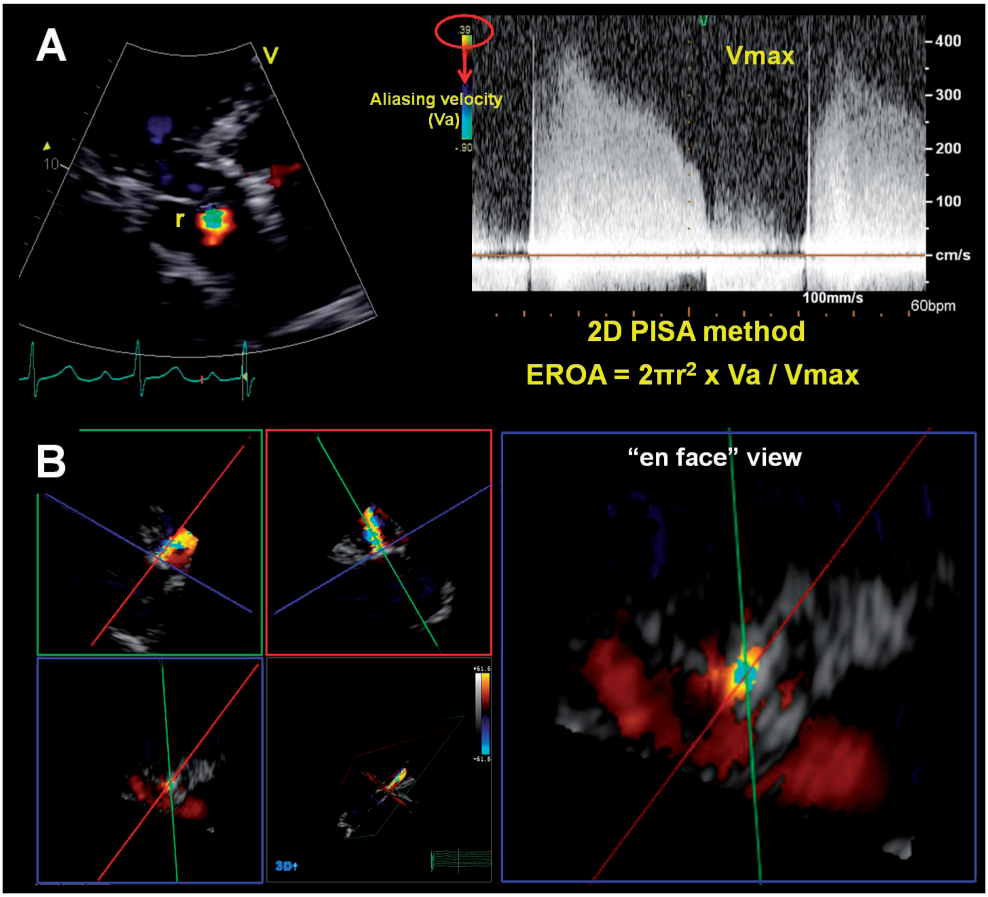

Figure 1. Quantitative assessment of aortic regurgitation severity using the proximal isovelocity surface area (PISA) method using conventional 2-dimensional Doppler echocardiography (panel A). Real-time 3-dmensional (3D) echocardiography permits unlimited plane orientation, allowing for the true cross-sectional area of the regurgitant jet to be planimetered, without multiple computation steps (panel B).

determine intervention in the current guidelines[5,6]) can be preserved until more advanced stage disease, as it lacks sensitivity in ascertaining the transition from compensated state to overt myocardial dysfunction and heart failure.[14,15] Hence, strain imaging using 2D STE may represent a promising tool, to detect subclinical myocardial dysfunction in patients with AV disease.

MULTIMODALITY IMAGING IN TAVI FOR TREATMENT OF AS

The critical steps in ensuring procedural success in TAVI are patient selection, sizing of prosthesis and procedural planning, and noninvasive multimodality imaging plays a key role in providing the important information involving the detailed 3D anatomy of AV, its spatial relationship with the coronary ostia and the ascending aorta, as well as the peripheral arteries. Advances in 3D echocardiography, complement with the superior spatial resolution of multi-

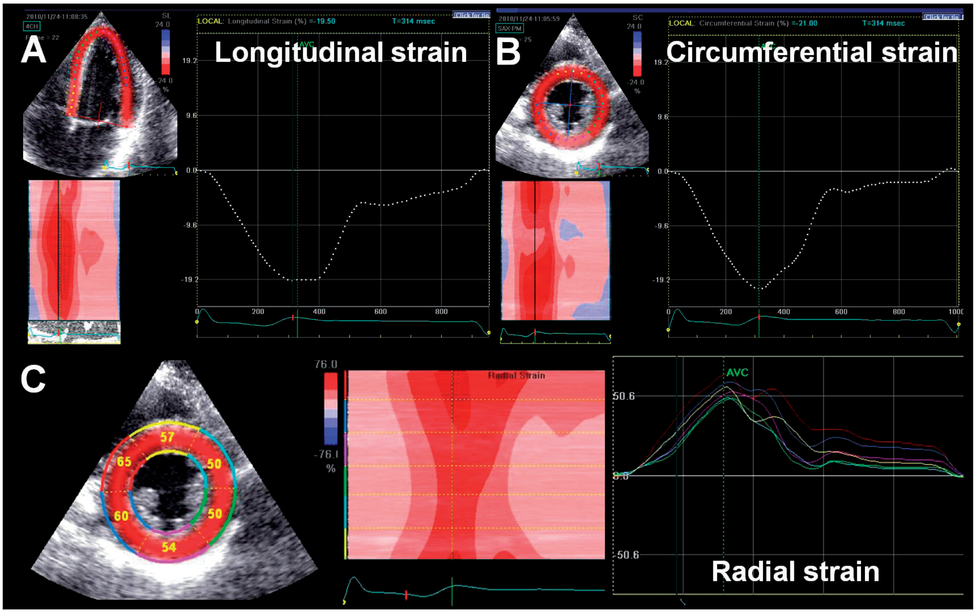

Figure 2. Two-dimensional speckle tracking echocardiography enables comprehensive assessment of active deformation of the myocardium in all 3 planes of cardiac motion, that is angle-independent on ultrasound insonation. Longitudinal strain (panel A) is calculated from apical views of the left ventricle (LV). Circumferential (panel B) and radial strain (panel C) are calculated from mid-ventricular short-axis views of the LV.

detector row computed tomography (MDCT) and magnetic resonance imaging (MRI) have enabled comprehensive pre-procedural evaluation, thus ensuring the best possible outcomes with TAVI.[26,27] However, as with any new technology, pitfalls and limitations are present in the currently used transcatheter valves. Paravalvular regurgitation (PVR) is frequent after TAVI and its presence has been associated with worse clinical outcomes.[28] Precise diagnosis and quantification of PVR is challenging, but advanced cardiac imaging provides insights into the understanding of the mechanism of PVR after TAVI, its assessment of severity, as well as its impact on outcomes over time. Finally, post-TAVI evaluation can also be systematically studied using cardiac imaging from several perspectives and in different patient groups.

OBJECTIVES AND OUTLINE OF THE THESIS

The objectives of this thesis were to investigate the role of advanced cardiac imaging modalities in the management of patients with AV diseases, and its clinical applications in transcatheter AV therapy.

In part I, the incremental value of novel imaging in patients with AR will be discussed. In particular, the additional diagnostic value of 3D echocardiography, over the conventional method of AR quantification using 2D Doppler echocardiography will be explored. Moreover, the value of 2D STE, over the conventional echocardiographic parameters to characterize LV performance in patients with chronic AR will be introduced.

Part II will focus on the clinical applications of multimodality cardiac imaging in TAVI for the treatment of severe AS. First, the evolving role of MDCT in the pre-procedural assessment and planning of patients undergoing transcathether valve therapy will be introduced. Next, the application of multimodality imaging in patient selection and procedural planning is proposed in the pre-TAVI evaluation algorithm.

After TAVI, the use of cardiac imaging to image, understand and quantify AR post-TAVI, and to guide further maneuvers intra-procedurally will be discussed. In addition, whether the AV calcium and its distribution, have an influence on AR after TAVI will be explored. Finally, the clinical and echocardiographic outcomes after TAVI will be further studied in patients with: 1) significant AR post-TAVI; 2) prosthesis-patient mismatch; 3) baseline impaired LV systolic function; 4) different procedural access, comparing transfemoral (TF) versus transapical (TA) approach.

REFERENCES

(1) Nkomo VT, Gardin JM, Skelton TN et al. Burden of valvular heart diseases: a population-based study. *Lancet* 2006;368:1005-1011.

(2) Iung B, Baron G, Butchart EG et al. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. *Eur Heart J* 2003;24:1231-1243.

(3) Iung B, Cachier A, Baron G et al. Decision-making in elderly patients with severe aortic stenosis: why are so many denied surgery? *Eur Heart J* 2005;26:2714-2720.

(4) Bonow RO, Carabello BA, Chatterjee K et al. 2008 Focused update incorporated into the ACC/AHA 2006 Guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2008;52:e1-e142.

(5) Vahanian A, Alfieri O, Andreotti F et al. Guidelines on the management of valvular heart disease (version 2012): The Joint Task Force on the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2012;33:2451-2496.

(6) Nishimura RA, Otto CM, Bonow RO et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;63:e57-e185.

(7) Lang RM, Badano LP, Mor-Avi V et al. Recommendations for cardiac chamber quantification by echocardiography in Adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015;16:233-271.

(8) Zoghbi WA, Enriquez-Sarano M, Foster E et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and doppler echocardiography. *J Am Soc Echocardiogr* 2003;16:777-802.

(9) Lancellotti P, Tribouilloy C, Hagendorff A et al. European Association of Echocardiography recommendations for the assessment of valvular regurgitation. part 1: aortic and pulmonary regurgitation (native valve disease). *Eur J Echocardiogr* 2010;11:223-244.

(10) Yosefy C, Hung J, Chua S et al. Direct measurement of vena contracta area by real-time 3-dimensional echocardiography for assessing severity of mitral regurgitation. *Am J Cardiol* 2009;104:978-983.

(11) Yingchoncharoen T, Agarwal S, Popovic ZB et al. Normal ranges of left ventricular strain: a meta-analysis. *J Am Soc Echocardiogr* 2013;26:185-191.

(12) Mignot A, Donal E, Zaroui A et al. Global longitudinal strain as a major predictor of cardiac events in patients with depressed left ventricular function: a multicenter study. *J Am Soc Echocardiogr* 2010;23:1019-1024.

(13) Stanton T, Leano R, Marwick TH. Prediction of all-cause mortality from global longitudinal speckle strain: comparison with ejection fraction and wall motion scoring. *Circ Cardiovasc Imaging* 2009;2:356-364.

(14) Olsen NT, Sogaard P, Larsson HBW et al. Speckle-tracking echocardiography for predicting outcome in chronic aortic regurgitation during conservative management and after surgery. *JACC Cardiovasc Imaging* 2011;4:223-230.

(15) Witkowski TG, Thomas JD, Debonnaire PJMR et al. Global longitudinal strain predicts left ventricular dysfunction after mitral valve repair. *Eur Heart J Cardiovasc Imaging* 2013;14:69-76.

(16) Leon M, Smith C, Mack M et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* 2010;363:1597-1607.

(17) Smith CR, Leon MB, Mack MJ et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl Med* 2011;364:2187-2198.

(18) Adams DH, Popma JJ, Reardon MJ et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *New Engl J Med* 2014;370:1790-1798.

(19) Dorosz JL, Lezotte DC, Weitzenkamp DA et al. Performance of 3-dimensional echocardiography in measuring left ventricular volumes and ejection fraction: a systematic review and meta-analysis. *J Am Coll Cardiol* 2012;59:1799-1808.

(20) Zamorano JL, Badano LP, Bruce C et al. EAE/ASE recommendations for the use of echocardiography in new transcatheter interventions for valvular heart disease. *Eur Heart J* 2011;32:2189-2214.

(21) Kahlert P, Plicht B, Schenk IM et al. Direct assessment of size and shape of noncircular vena contracta area in functional versus organic mitral regurgitation using real-time three-dimensional echocardiography. *J Am Soc Echocardiogr* 2008;21:912-921.

(22) Marsan NA, Westenberg JJM, Ypenburg C et al. Quantification of functional mitral regurgitation by real-time 3D echocardiography: comparison with 3D velocity-encoded cardiac magnetic resonance. *JACC Cardiovasc Imaging* 2009;2:1245-1252.

(23) Korinek J, Wang J, Sengupta PP et al. Two-dimensional strain - a Doppler-independent ultrasound method for quantitation of regional deformation: validation in vitro and in vivo. *J Am Soc Echocardiogr* 2005;18:1247-1253.

(24) Leitman M, Lysyansky P, Sidenko S et al. Two-dimensional strain-a novel software for real-time quantitative echocardiographic assessment of myocardial function. *J Am Soc Echocardiogr* 2004;17:1021-1029.

(25) Stanton T, Marwick TH. Assessment of subendocardial structure and function. *JACC Cardiovasc Imaging* 2010;3:867-875.

(26) Bax JJ, Delgado V, Bapat V et al. Open issues in transcatheter aortic valve implantation. Part 1: patient selection and treatment strategy for transcatheter aortic valve implantation. *Eur Heart J* 2014;35:2627-2638.

(27) Bax JJ, Delgado V, Bapat V et al. Open issues in transcatheter aortic valve implantation. Part 2: procedural issues and outcomes after transcatheter aortic valve implantation. *Eur Heart J* 2014;35:2639-2654.

(28) Athappan G, Patvardhan E, Tuzcu EM et al. Incidence, predictors, and outcomes of aortic regurgitation after rranscatheter aortic valve replacement: meta-analysis and systematic review of literature. *J Am Coll Cardiol* 2013;61:1585-1595.